Effect of GR32191, a potent thromboxane receptor antagonist, on exercise induced bronchoconstriction in asthma

J P Finnerty, O P Twentiman, A Harris, J B D Palmer, S T Holgate

Abstract
Previous work suggests a role for mast cell derived mediators in exercise induced asthma. The contribution of newly generated contractile prostaglandins to exercise induced asthma was assessed by using a potent and orally active thromboxane (TP), receptor antagonist, GR32191. The effect of 120 mg GR32191 on exercise induced asthma was observed in 12 asthmatic subjects. For the exercise challenge the subjects performed six minutes of treadmill exercise, breathing dry air at a work load that had previously been shown to induce a fall in FEV\(_1\), of 25% or more from the pre-exercise baseline. No effect of GR32191 on pre-exercise baseline airway calibre was evident. There was no significant difference in the mean maximum percentage fall in FEV\(_1\) from baseline after exercise between drug and placebo (placebo 30-2%, GR32191 day 31-6%). It is concluded that the thromboxane antagonist GR32191 has no effect on exercise induced asthma. This suggests that prostaglandins, including PGD\(_2\), that act via the thromboxane receptor do not have an important role in exercise induced asthma.

Exercised induced bronchoconstriction in asthma is believed to be due, at least in part, to degranulation of airway mast cells, possibly as a result of transient hypertonicity of the airway lining fluid.\(^1\)\(^2\) The role of the mast cell has been suggested by studies showing that exercise induced asthma can be suppressed by prior administration of sodium cromoglicate and nedocromil sodium, and partially inhibited by selected H\(_1\) antihistamines.\(^3\)\(^5\)

Placing hypertonic solutions in the Airways has been shown to stimulate the generation and release in vivo of prostaglandin D\(_2\) (PGD\(_2\)),\(^6\) a potent bronchoconstrictor, in addition to releasing preformed mediators such as histamine. We have shown that the selective cyclo-oxygenase inhibitor flurbiprofen attenuates exercise induced asthma, and this is believed to be through reduction of the endogenous generation of prostanoids, including thromboxane A\(_2\) (TxA\(_2\)) and PGD\(_2\).\(^5\) Previous studies using indomethacin have failed to show any effect on exercise induced asthma.\(^8\)\(^9\) PGD\(_2\) mediated contraction of human bronchial smooth muscle is thought to be mediated via a specific thromboxane TP receptor.\(^10\) The compound GR32191 is a potent orally active competitive TP receptor antagonist, which has been shown to protect the airways of patients with asthma against the bronchoconstrictor effect of inhaled PGD\(_2\), and to reduce the immediate bronchoconstrictor response to inhaled allergen.\(^11\) In this study we determined the direct contribution of contractile prostaglandins to the airway narrowing provoked by exercise, using GR32191 in a dose of 120 mg.

Methods

SUBJECTS

Twelve non-smoking asthmatic volunteers (nine male, mean age 28-8, range 19-45 years) took part (table). All were known to have exercise induced asthma. None had had a respiratory tract infection or required any change in medication within a month of entering the study, and none had required oral corticosteroids within the previous six months. All had a baseline FEV\(_1\), of at least 60% of the predicted value on entry to the study, and all gave written informed consent. Before study visits inhaled beta\(_2\) agonists and sodium cromoglicate were withheld for at least six hours and inhaled corticosteroids for at least 12 hours. The study was approved by the Southampton University and hospitals ethical subcommittee.

EXERCISE CHALLENGE

Subjects exercised on an electrically driven...
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Protocel

Before entry to the study a treadmill exercise task sufficient to induce at least a 25% fall in FEV₁ from the level immediately before exercise was determined for each subject. The exercise study day visits were at least five and no more than 14 days apart. After the subject had rested for five minutes baseline FEV₁ was measured, the highest of three technically satisfactory readings being used. Either GR32191 120 mg or matched placebo tablets were then administered, the order being randomised. One hour later the pre-exercise baseline FEV₁ was measured, and this was followed by a six minute exercise test. Measurements of FEV₁ were made over the next 30 minutes. Any residual bronchoconstriction was reversed with inhaled salbutamol 200 μg.

Data Analysis

The maximum percentage fall in FEV₁ from baseline, pre-exercise FEV₁ values, and volume respired during exercise on the two study days were compared by the paired Student’s t test, significance being attributed at the 5% level. The power of the study to detect a change in the maximum percentage fall in FEV₁ after exercise was calculated from standard statistical tables; for this we used a standard deviation (11-9%) derived from data from the placebo day and from a prestudy control day on the 12 subjects. This figure is consistent with the repeatability of exercise induced bronchoconstriction found by other workers.

Results

The mean (SEM) FEV₁ values before and one hour after GR32191 were 3-69 (0-22) l before GR32191 and 3-67 (0-24) l one hour afterwards (NS). The mean baseline value of FEV₁ immediately before exercise did not differ between the two study days (3-75 (0-22) v 3-67 (0-24) l). There was no significant difference in ventilation over the six minutes of exercise on the two study days (215 (11) l on the placebo day v 220 (12) l on the GR32191 day).

The maximum percentage fall in FEV₁ from the pre-exercise level after oral placebo was 30-2% (3-6%). Neither the maximum fall in FEV₁ nor the time course of bronchoconstriction differed significantly between placebo and GR32191 (figure and table). Neither a period effect nor a treatment-period interaction was evident. The study had a greater than 80% power of showing a 35% inhibition of the mean maximum percentage fall in FEV₁.

Discussion

Using an antagonist of thromboxane TP₁ receptors, we have attempted for the first time to separate the component of bronchoconstriction in exercise induced asthma resulting from release of contractile prostaglandins. GR32191 failed to have any significant effect on the magnitude or time course of exercise induced asthma. These data do not support a role for contractile prostaglandins, including mast cell derived PGD₂, in exercise induced asthma.

Using human bronchial muscle preparations, Coleman and Sheldrick have shown that U-46619, a stable thromboxane mimetic, is the most potent prostanooid contractile agonist, being 383 fold and 628 fold more potent on a molar basis than PGF₂α and PGD₂. As the competitive antagonist AH23848 displaced the dose-response curves for all these prostaglandins to a similar degree they suggested that the prostaglandins mediate their bronchoconstrictor effect via the same receptor, the thromboxane prostaglandin receptor (TP). Armour et al. found that GR32191, an analogue of AH23848, potently inhibited contractions induced by PGF₂α and U-46619 in human bronchial rings, and also protected
against the contractile but not the relaxant effect of PGE,

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PGF,

of TP, the against the was inhibited after 80 mg of oral PGD induced broncho-

activity in vivo on vascular contractile concentrations of up to 0-1 traction, with an estimated two fold shift to the right of the dose-response curve at a concentration of the antagonist in the nanomolar range. No effect on methacholine induced contraction was observed at the highest concentration of GR32191 given. The specificity of GR32191 in vitro has been confirmed by other investigators; it does not protect against bronchial muscle contraction induced by carbobach,

histamine, 5-hydroxytryptamine, or potassium chloride at concentrations of up to 0-1 mmol. Vasoconstriction by intravenous PGF, was ablated by a 20 mg oral dose of GR32191, showing its activity in vivo on vascular contractile TP receptors. PGD induced bronchoconstriction was inhibited after 80 mg of oral GR32191, with a mean 10 fold displacement of the dose-response curve to the right. Thus GR32191 is a potent and specific antagonist at the TP, receptor in man. In the present study in patients with asthma, GR32191 failed to increase baseline FEV with, indicating that contractile prostanooids probably have little influence on resting airway tone. All the subjects studied had an exercise induced fall in FEV, and this did not differ significantly in magnitude or time course after GR32191 and placebo. These data suggest that contractile prostanooids have little or no role in the pathogenesis of exercise induced asthma. This finding accords with the work of O'Byrne and Jones, who found no inhibition of exercise induced bronchoconstriction with indomethacin. It is, however, in conflict with our previous findings with flurbiprofen, a more potent cyclo-oxygenase inhibitor, which probably have little influence on resting airway tone. Potentially have little or no role in the pathogenesis of exercise induced asthma.

PGF,

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